Theoretical Study of Ester Enolate–Imine Condensation Route to β-Lactams

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ABSTRACT: The condensation reaction of the enolate of methyl acetate with formaldimine to afford a β-lactam was studied using the MP2-FC/6-31+G* level of theory taking into account the electrostatic effect of the solvent by means of a self-consistent reaction field continuum model. The reaction is a stepwise process with three main steps: the formation of the C3—C4 bond, the closure of the β-lactam ring, and the elimination of the methoxide ion. The formation of the C3—C4 bond is rate determining and according to our calculations is not a reversible step. © 1998 John Wiley & Sons, Inc. J Comput Chem 19: 1826–1833, 1998

Keywords: quantum–chemical computations; β-lactams; ester enolate–imine condensation; solvent effect; stepwise process

Introduction

β-lactams are key components of many biologically active compounds such as cephalosporin and penicillin antibiotics and are also powerful precursors for the synthesis of different natural and unnatural products.[1] The [2 + 2] cycloaddition reaction between ketenes and imines, known as the Staudinger reaction, is the most common procedure for constructing the β-lactam ring.[1c] An alternative approach to synthesize β-lactams is based on the condensation reaction of ester enolates with imines.[2] The ester enolate–imine condensation appears to be very complex. By a proper choice of metal, solvent, and substituents, *cis* or *trans* β-lactams can be selectively synthesized in high yields. When chiral ester enolates or

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imines are used, asymmetric induction occurs to yield optically active β-lactams with enantiomeric or diastereomeric excesses that also depend on the metal, solvent, and substituents. According to experimental findings, the condensation reaction of ester enolates with imine is a two-step process (see Scheme 1).[2a] The first step of the reaction corresponds to the formation of the C3—C4 bond to give a β-amino ester. The second one consists of a nucleophilic cyclization to give the β-lactam by means of the formation of the N1—C2 bond and the loss of R_5O^-. An important issue of the mechanism is the rate-determining step. For instance, the results obtained when Reformatsky reagents are treated with *N*-arylaldimines or *N*-alkylaldimines were interpreted as evidence for a condensation cyclization mechanism in which the cyclization was rate determining.[2a] On the other hand, studies with some β-amino esters suggest that the azomethine addition is the rate-determining step in many lithium enolate–imine condensations conducted in tetrahydrofuran.[2a,3] A second important mechanistic issue to explain the stereochemical course of this reaction is the reversibility of the ester–imine condensation or the reversibility of the first step when this is the rate-determining one.

In spite of its synthetic interest the mechanism of this condensation reaction has not yet been fully investigated theoretically. According to a previous *ab initio* study the construction of β-lactams through the reaction of α-hydroxyl lithium ester enolates with imine proceeds through an initial complex and a boatlike transition structure connecting this complex with an intermediate that in turn evolves to the products.[4] The incorporation of a single solvent molecule (ammonia) has no significant effect on the transition state geometry.

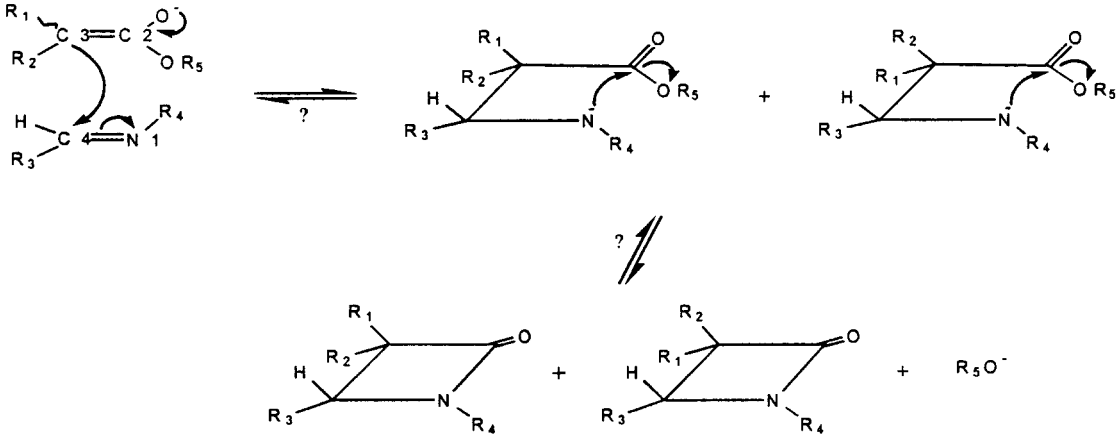
An alternative mechanism to that proposed in Scheme 1 would pass through the fragmentation of the ester enolate to afford a ketene that would then undergo a cycloaddition with the imine to give a β-lactam. However, this mechanistic proposal was ruled out according to stereochemical results.[2a,3] Note however that such an alternative mechanism cannot be completely rejected in some cases.[2a]

As a first step toward a deeper understanding of the mechanism of the ester enolate–imine condensation route, we undertake an *ab initio* study of the mechanism shown in Scheme 1 for the reaction between the free enolate of methyl acetate and formaldimine. We particularly focus our attention on the two mechanistic issues mentioned: the rate-determining step and its reversibility. A thermodynamical analysis of the computational results obtained was performed and the electrostatic effect of solvent was taken into account in order to properly rationalize the experimental findings.

The role of the counterion was not taken into account in this work whose main objective was to make a preliminary study of the reaction, including solvent effects. However, some comparison with previous studies in which the counterion was explicitly considered is presented below.

Computational Methods

Quantum-chemical computations were carried out with the Gaussian 94 system of programs[5] in which extra links for the solvent effect treatment were added.[6] In the gas phase, structures were fully optimized and transition structures (TSs) were located by Schlegel's algorithm[7] at the Hartree–Fock (HF), MP2-FC, and density functional theory



SCHEME 1

(DFT) (B3LYP[8]) levels by using the 6-31 + G* basis set.[9] Harmonic vibrational frequencies were calculated at the B3LYP[10] level in order to characterize the critical points located and to evaluate the zero-point vibrational energies (ZPVE). Intrinsic reaction coordinate (IRC)[11] calculations at the HF/6-31 + G* level starting at each saddle point verified the two minima connected by that TS.

Enthalpy, entropy, and free energy values were calculated to obtain results more readily comparable with the experiment. These magnitudes were computed within the ideal gas, rigid rotor, harmonic oscillator approximations.[12] A temperature of 195.15 K and a pressure of 1 atm were assumed in the calculations.

In solution MP2-FC single point computations were carried out on the MP2 geometries optimized in the gas phase. We used a general self-consistent reaction field (SCRF) model proposed for quantum chemical computations on solvated molecules.[13] In this model the solvent is represented by an infinite dielectric continuum, characterized by its dielectric relative permittivity, ϵ, in which a cavity is created and the solute is placed in it. The charge distribution of the solute polarizes the continuum that in turn creates an electric field inside the cavity. Accordingly, the charge distribution and the geometry of the solute will change until equilibrium is reached. The SCRF continuum model employed assumes a general cavity shape that is obtained using van der Waals solute atomic spheres with modified radii ($1.3084 * r_{vdW}$), which is necessary to fulfill the volume condition,[13a] and a monocentric multipolar expansion of the electrostatic solvation energy.[13] A relative permittivity of 7.58 was used to simulate solvents commonly used in the experimental work.

The use of a cavity model generally leads to a reasonable prediction of electrostatic effects. It was used to investigate charge separation reactions[13d] with results comparable to those derived from more sophisticated solvent models such as Monte Carlo simulations.[14] The main limitations are related to the difficulty of computing nonelectrostatic energies, but the variation of such contributions along the reaction coordinate is expected to be negligible compared to the variation of electrostatic interactions in the present reaction. Another limitation lies in the difficulty of defining the cavity volume of anionic species. Tuñón et al.[15] proposed that this volume should be smaller than that for an equivalent neutral system because the first solvation shell is expected to strongly interact with the solute. However, it is not easy to accurately account for these specific interactions by simply decreasing the cavity volume, which in addition may produce instabilities in the SCF procedure. Thus, in our calculations the volume is computed as usual for neutral molecules (i.e., our solvation energies may be a little underestimated).

Results and Discussion

REACTION MECHANISM *IN VACUO*

According to our calculations the ester enolate–imine condensation reaction to afford a β-lactam takes place with a stepwise mechanism. The geometries of the critical structures located are displayed in Figures 1 and 2. The relative energies and the ZPVE correction for these structures are collected in Table I. Unless otherwise stated, the energies given in the text are those corresponding to the MP2-FC/6-31 + G* level including the ZPVE correction calculated from the B3LYP/6-31 + G* unscaled frequencies.

The first critical structure located along the reaction coordinate corresponds to a complex, **C**,

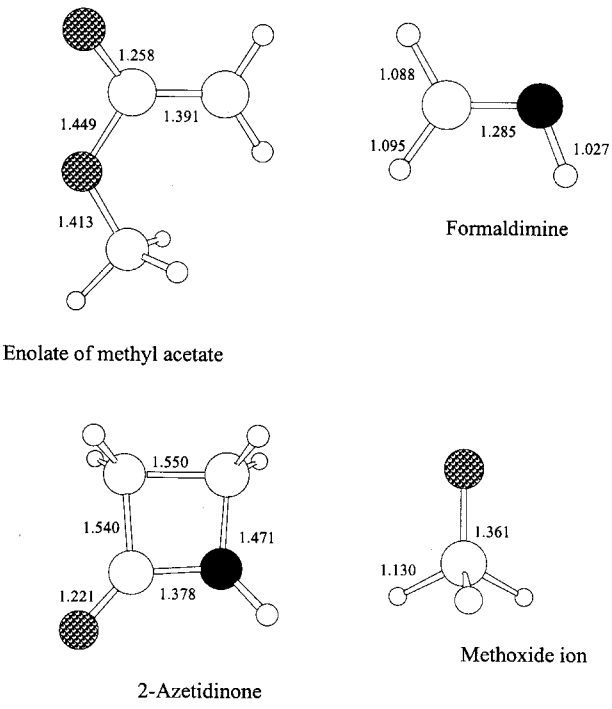


FIGURE 1. MP2-FC / 6-31 + G* optimized geometries of the stable structures located along the reaction coordinate for the condensation reaction of the enolate of methyl acetate with formaldimine. Distances are given in angstroms.

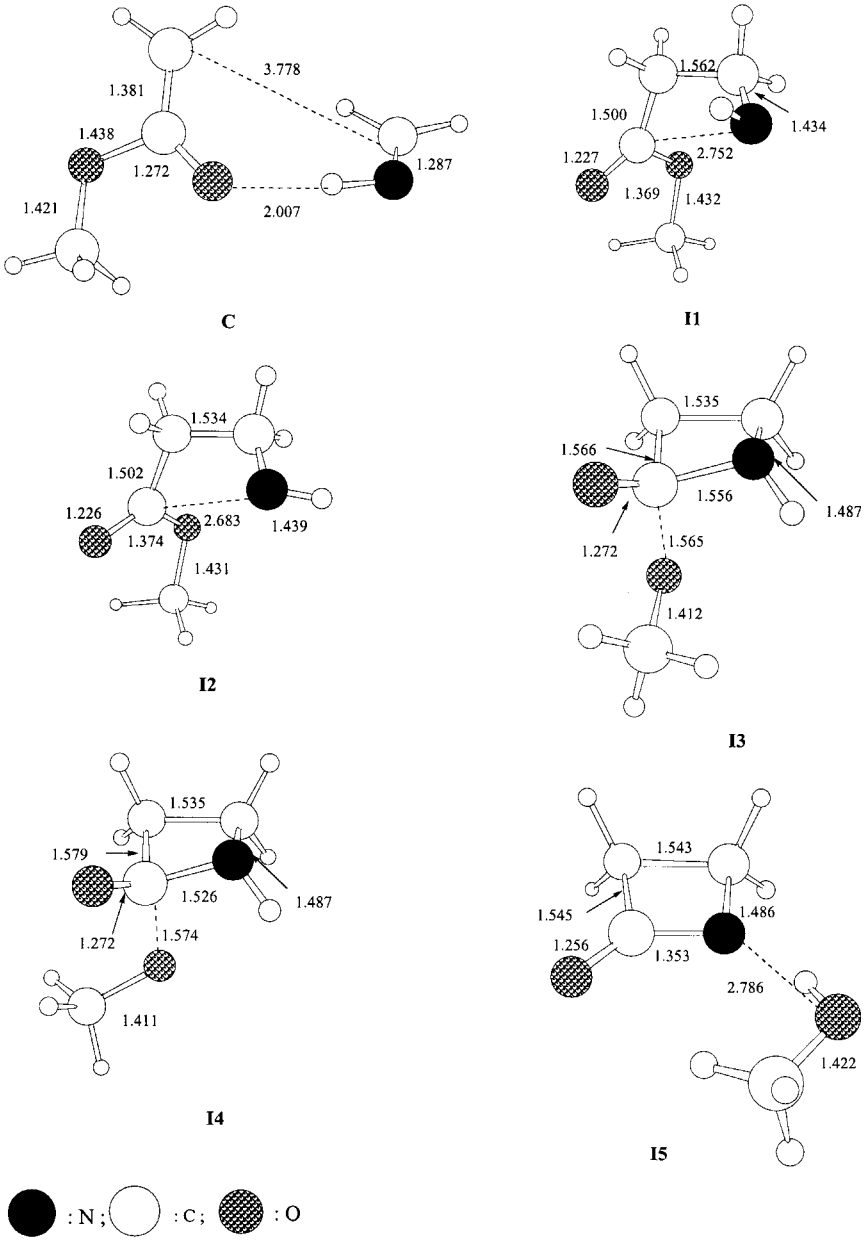


FIGURE 1. (Continued)

between the enolate and formaldimine. This complex presents an NH···O hydrogen bond with an H—O distance of 2.007 Å and is 17.1 kcal/mol more stable than reactants. This complex evolves through a gauche TS 16.9 kcal/mol higher in energy, **TSC1**, for the formation of the C3–C4 bond giving a β-amino ester, **I1**, which is 4.4 kcal/mol more stable than reactants. At **TSC1** the C3—C4 forming bond distance is 1.946 Å whereas the N1—C2 distance is 2.886 Å. This C3—C4 distance compares favorably with the values of 2.070–2.073 Å obtained for boatlike TSs located at the HF/3-21G level for the reaction of α-hydroxyl lithium ester enolate with imine[4] in which the role of a counterion, Li^+, was explicitely taken into account. At **I1** the C3—C4 and N1—C2 distances are 1.562 and 2.752 Å, respectively. This **I1** leads to another conformation of the β-amino ester, **I2**, that is 0.9 kcal/mol higher in energy through a TS, **TS12**, for the rotation of the N1—H bond about the N1—C4 bond with an energy barrier of 2.1 kcal/mol. The cyclization of **I2**

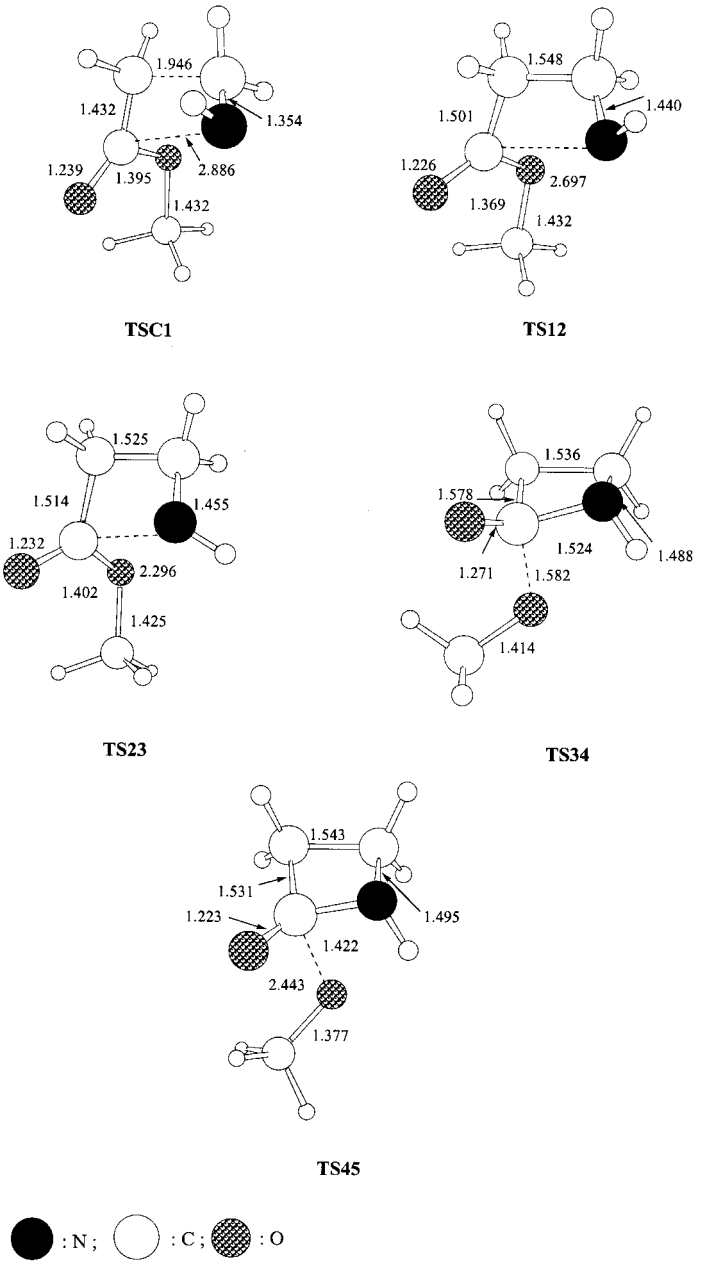


FIGURE 2. MP2-FC / 6-31+G* transition structures located along the reaction coordinate for the condensation reaction of the enolate of methyl acetate with formaldimine. Distances are given in angstroms.

through a TS, **TS23**, which is 1.1 kcal/mol higher in energy, gives an intermediate, **I3**, that is 12.7 kcal/mol more stable than reactants. At **TS23** the N1–C2 distance is 2.296 Å. At **I3** the N1—C2 bond is almost completely formed with a bond distance of 1.556 Å whereas the C2—OCH_3 distance is slightly elongated. **I3** is in turn connected with another very similar intermediate, **I4**, which is 1.0 kcal/mol more stable than is through a TS, **TS34**, with an energy barrier of 0.4 kcal/mol corresponding to a displacement of the H_3CO^- moiety toward the outer part of the system. Finally, **I4** evolves through a TS, **TS45**, that is 5.3 kcal/mol higher in energy for the elimination of the H_3CO^- moiety from C2 and its attachment to the hydrogen atom originally bonded to N1 giving an intermediate, **I5**, that could be described as a cyclic $NCO(CH_2)_2$ anion solvated with a molecule of methanol. This solvated anion is 32.2 kcal/mol more stable than reactants and 41.3 kcal/mol more

TABLE I.
Total (hartree) and Relative (kcal / mol) Energies at MP2-FC / 6-31 + G* Theory Level and ZPVE Corrections (kcal / mol) at B3LYP / 6-31 + G* Theory Level for Chemically Important Structures Located on Ester Enolate – Imine Condensation Reaction.

Species	Total Energy	ZPVE	Relative Energy
Reactants	−361.30311	64.55	0.0
C	−361.33194	65.59	−18.1
TSC1	−361.30619	66.29	−1.9
I1	−361.31383	66.85	−6.7
TS12	−361.31020	66.68	−4.4
I2	−361.31257	66.90	−5.9
TS23	−361.31069	66.91	−4.8
I3	−361.32828	67.65	−15.8
TS34	−361.32734	67.48	−15.2
I4	−361.33010	67.80	−16.9
TS45	−361.31980	66.65	−10.5
I5	−361.35821	66.93	−34.6
Products	−361.28915	64.88	8.8

The total energies in hartrees for the reactants, enolate of methyl acetate and formaldimine, are −266.97997 and −94.32314, respectively, and for the products, 2-azetidinone and methoxide ion, are −246.54462 and −114.74453, respectively.

stable than 2-azetidinone + H_3CO^-. It is interesting to note that when the electronic correlation is not taken into account at the HF/6-31 + G* level the hydrogen atom remains attached to N1 and the H_3CO^- moiety interacts with it with a $N1H\cdots OCH_3$ distance of 1.564 Å. Then according to these results the electronic energy profile for this process proceeds under the energy level corresponding to reactants, the intermediate **I5** being much more stable than 2-azetidinone + H_3CO^-, which are 9.1 kcal/mol above the reactants.

As indicated above we used standard procedures to evaluate relative free energies at 195.15 K and 1 atm conditions. We see in Table II that, in general, relative enthalpies are larger than relative electronic energies all along the reaction coordinate. From **C** to **TS23** the increment corresponds to 2.2–4.1 kcal/mol whereas from **I3** to **I4** the maximum increase of 4.6–5.4 kcal/mol appears. For 2-azetidinone + H_3CO^- ΔH is only 0.4 kcal/mol greater than ΔE_{elec}. Entropy contributions disfavor the reaction. From **TSC1** to **TS45** the entropic factor amounts to 7.2–8.5 kcal/mol while for **C** and **I5** it is about 5 kcal/mol. For 2-azetidinone + H_3CO^- the $-T\Delta S$ is only 0.4 kcal/mol. These contributions give a free energy profile in which the structures from **TSC1** to **TS23** and **TS45** are less stable than reactants rendering an energy barrier of 19.2 kcal/mol from **C** for **TSC1** that is the rate-determining TS. **I5** remains the most stable structure along the reaction coordinate (−24.8 kcal/mol) and 2-azetidinone + H_3CO^- are 9.6 kcal/mol above the reactants.

REACTION MECHANISM IN SOLUTION

MP2-FC/6-31 + G* SCRF single point calculations were performed on the MP2-FC/6-31 + G* optimized gas-phase geometries for all the critical

TABLE II.
Relative MP2-FC / 6-31 + G* Energy (ΔE_{elec}), Zero-Point Vibrational Energy Correction (ΔE_{ZPVE}), Thermal Energy (ΔE_t), Enthalpy (ΔH), Entropy Contribution ($-T\Delta S$), Gibb's Free Energy in Vacuum (ΔG_{vacuum}), Electrostatic Free Energy of Solvation (ΔG_{ES}), and Gibb's Free Energy in Solution ($\Delta G_{solution}$) (kcal / mol) for Chemically Important Structures Located on Ester Enolate – Imine Condensation Reaction.[a]

Species	R[b]	C	TSC1	I1	TS12	I2	TS23	I3	TS34	I4	TS45	I5	P[b]
Gas Phase													
ΔE_{elec}	0.0	−18.1	−1.9	−6.7	−4.4	−5.9	−4.8	−15.8	−15.2	−16.9	−10.5	−34.6	8.8
ΔE_{ZPVE}	0.0	1.0	1.7	2.3	2.1	2.4	2.4	3.1	2.9	3.2	2.1	2.4	0.3
ΔE_t	0.0	1.6	1.5	2.1	1.8	2.1	1.7	2.5	2.1	2.6	1.7	2.5	0.05
ΔH	0.0	−15.9	0.9	−2.7	−0.9	−1.8	−1.1	−10.6	−10.6	−11.5	−7.1	−30.1	9.2
$-T\Delta S$	0.0	4.8	7.2	7.2	7.6	7.6	8.3	8.2	8.5	8.4	7.8	5.3	0.4
ΔG_{vacuum}	0.0	−11.1	8.1	4.5	6.7	5.8	7.2	−2.4	−2.1	−3.1	0.7	−24.8	9.6
Solution													
ΔG_{ES}	−60.7	−48.8	−52.2	−62.1	−59.1	−61.2	−57.3	−54.5	−54.3	−54.5	−50.2	—	−71.3
$\Delta G_{solution}$	0.0	0.8	16.6	3.1	8.3	5.3	10.6	3.8	4.3	3.1	11.2	—	−1.0

[a] 195.15 K, 1 atm; $\Delta H = \Delta E_{elec} + \Delta E_{ZPVE} + \Delta E_t + \Delta nRT$, $\Delta G_{vacuum} = \Delta H - T\Delta S$; $\Delta G_{solution} = \Delta G_{vacuum} + \Delta G_{ES}$.
[b] The electrostatic solvation energies (kcal / mol) for enolate of methyl acetate, formaldimine, 2-azetidinone, and methoxide ion are −57.0, −3.7, −5.4 and −65.9, respectively.

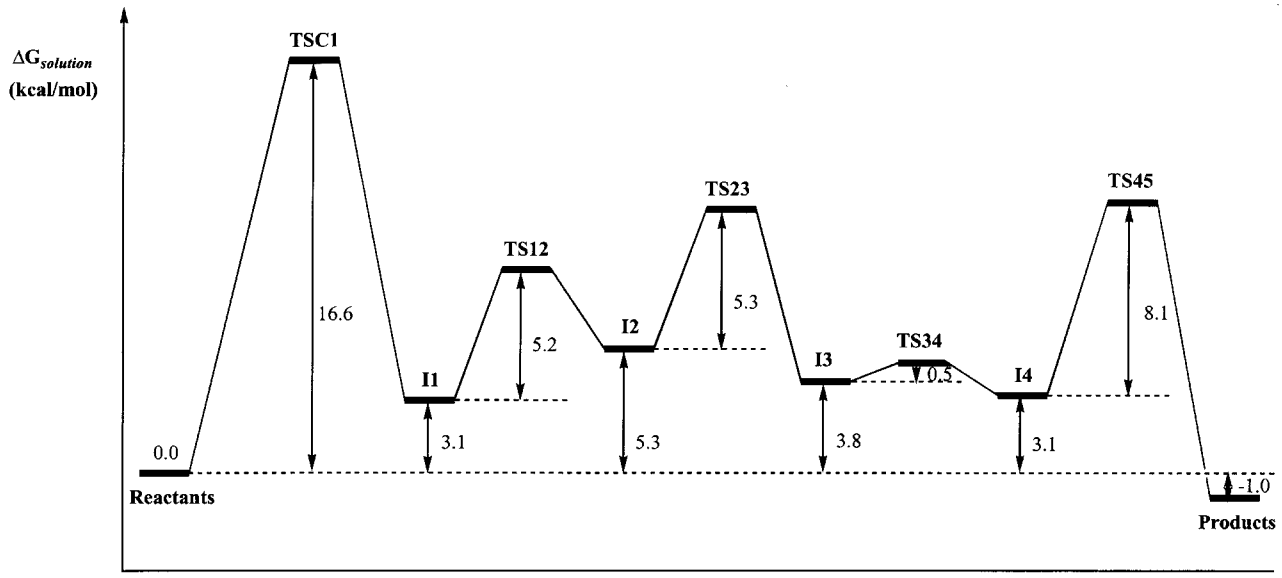


FIGURE 3. Free energy profile for the ester enolate condensation reaction of the enolate of methyl acetate in solution ($\epsilon = 7.58$).

structures along the reaction coordinate using a dielectric permittivity of 7.58. Figure 3 displays the free energy profile thus obtained in solution.

The most stabililized structures through the electrostatic effect of the solvent are the reactants, **I2**, **I1**, and above all 2-azetidinone + H_3CO^- because of the smaller size of the methoxide ion (see Table II). The greater stabilization in solution of 2-azetidinone + H_3CO^- than the reactants renders the process exoergic by 1.0 kcal/mol. The inclusion of the electrostatic free energy of solvation causes **C** to be less stable than the reactants, thus it disappears as a minimum structure on the potential energy surface in solution. **TSC1** remains the rate-determining TS in solution with a free energy barrier of 16.6 kcal/mol, given that it becomes less stabilized by the electrostatic effect of solvent than **TS12**, **TS23**, and **TS34**. Nevertheless, the less favored TS by the interaction with the solvent is **TS45** that presents in solution a free energy barrier of 11.2 kcal/mol, which is much greater than that in the gas phase (3.8 kcal/mol).

Given the large stabilization of 2-azetidinone + H_3CO^- by solvent interaction one could raise the question whether **I5** still remains a minimum structure in the energy profile for the ester enolate–imine condensation reaction to give 2-azetidinone + H_3CO^- in solution. In order to investigate this point, as well as the detailed mechanism for the cleavage of the C2—OCH_3 bond to eliminate the methoxide ion, we performed full geometry optimization in solution of reactants, 2-azetidinone, H_3CO^-, and structures **TS45** and **I5** at the HF/6-31G* SCRF ($\epsilon = 7.58$) level. Single point calculations at the MP2-FC/6-31+G* SCRF level were carried out on these HF optimized geometries to obtain a better estimation of the stability of **TS45** with respect to reactants and products. The results obtained in solution show that at this theory level **TS45** is a saddle point that is 10.0 kcal/mol less stable than reactants, and the elimination of the methoxide ion takes place after the closure of the β-lactam ring. The optimized geometry of **TS45** in solution is very similar to the gas-phase one. In contrast, all the attempts to locate **I5** failed so that **TS45** is now directly connected with the products of the reaction. The process remains exoergic by 1.7 kcal/mol.

According to our results in solution (see Fig. 3) the rate-determining first step is not reversible. Nevertheless, the presence of appropriate substituents could increase the mean life of **I1**, thus making possible the equilibration of the internal energy of this intermediate and facilitating the regeneration of enolate and imine.[16]

In summary, the condensation reaction of the enolate of methyl acetate and formaldimine is a stepwise process. The three main steps correspond to the formation of the C3—C4 bond, the cyclization through the formation of the N1—C2 bond, and the elimination of the methoxide ion. Therefore, the cyclization and the elimination of the

methoxide ion take place at different steps of the reaction. The rate-determining step corresponds to the formation of the C3—C4 bond with an energy barrier of 16.6 kcal/mol. According to the free energy profile obtained from our calculations in solution, the first step of the mechanism is not reversible.

Acknowledgments

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